Complete Summary

GUIDELINE TITLE

HIV drug - drug interactions.

BIBLIOGRAPHIC SOURCE(S)

New York State Department of Health. HIV drug-drug interactions. New York (NY): New York State Department of Health; 2008 Mar. 48 p. [32 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: New York State Department of Health. HIV drug-drug interactions. New York (NY): New York State Department of Health; 2007 Feb. 44 p.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

- March 12, 2008, Prezista (darunavir): The U.S. Food and Drug Administration (FDA) and Tibotec Therapeutics notified healthcare professionals of changes to the WARNINGS section of the prescribing information for Prezista (darunavir) tablets regarding the risk of hepatotoxicity, specifically, drug induced hepatitis in patients receiving combination therapy with Prezista/ritonavir.
- October 18, 2007, PDE5 inhibitors, Viagra (sildenafil citrate), Levitra (vardenafil HCL), Cialis (tadalafil): The PRECAUTION and updated Adverse Reactions Sections of the approved product labeling for Viagra, Levitra, and Cialis were revised in response to reports of sudden decreases or loss of hearing.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Human immunodeficiency virus (HIV) infection
- Conditions associated with drug interactions encountered in HIV-infected patients using highly active antiretroviral therapy (HAART) as well as therapy for comorbid conditions and for prophylaxis of opportunistic infections

GUIDELINE CATEGORY

Counseling
Management
Prevention
Risk Assessment

CLINICAL SPECIALTY

Allergy and Immunology
Family Practice
Infectious Diseases
Internal Medicine
Pharmacology
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Health Care Providers
Pharmacists
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To provide an overview of known and potential drug interactions encountered with the use of highly active antiretroviral therapy (HAART)
- To provide recommendations for prevention and management of these drug interactions

TARGET POPULATION

Human immunodeficiency virus (HIV)-infected patients

INTERVENTIONS AND PRACTICES CONSIDERED

1. Thorough medication history at each visit including prescription medications, over-the-counter medications, recreational drugs, and herbal and alternative therapies
2. Classification of common substrates, inducers, and inhibitors of the cytochrome P-450 (CYP450) system to predict significant drug interaction
3. Identification of dietary restrictions with antiretroviral (ARV) drugs to avoid food-drug interactions
4. Provision of detailed list of drugs contraindicated with the use of highly active antiretroviral therapy (HAART)
5. Avoidance of certain drug combinations (refer to the original guideline document for details)
6. Dose adjustments during HAART regimens

MAJOR OUTCOMES CONSIDERED

Morbidity/adverse effects associated with drug-drug interactions

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

AIDS Institute clinical guidelines are developed by distinguished committees of clinicians and others with extensive experience providing care to people with HIV infection. Committees* meet regularly to assess current recommendations and to write and update guidelines in accordance with newly emerging clinical and research developments.

The Committees* rely on evidence to the extent possible in formulating recommendations. When data from randomized clinical trials are not available, Committees rely on developing guidelines based on consensus, balancing the use of new information with sound clinical judgment that results in recommendations that are in the best interest of patients.

* Current committees include:

- Medical Care Criteria Committee
- Committee for the Care of Children and Adolescents with HIV Infection
- Dental Standards of Care Committee
- Mental Health Committee
- Women's Health Committee
- Substance Use Committee
- Physician's Prevention Advisory Committee
- Pharmacy Committee

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

All guidelines developed by the Committee are externally peer reviewed by at least two experts in that particular area of patient care, which ensures depth and quality of the guidelines.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The clinician should conduct a thorough medication history at each visit that includes prescription medications, including those prescribed by other providers, over-the-counter medications, recreational drugs, and herbal/alternative therapies.

The clinician should classify common substrates, inducers, and inhibitors of the cytochrome P-450 (CYP450) system used in highly active antiretroviral therapy (HAART) to accurately predict drugs that may lead to significant drug interactions (refer to Table below titled "Select CYP450 Inducers, Inhibitors, and Substrates").

Refer to Appendix B in the original guideline document for information on routes of elimination of HAART and the effect on CYP450.

The clinician should identify dietary restrictions with antiretroviral (ARV) drugs so that food-drug interactions can be avoided.

Key Points:

- Clinicians should instruct their patients to notify them of any new medication the patient is taking.
- Providing patients with a detailed list of drugs that are contraindicated with HAART may help the patient to identify significant drug interactions.

Classification of Drug Interactions

Key Point:

Induction can be problematic during HAART due to concerns for virologic failure when protease inhibitors (PI) and/or non-nucleoside reverse transcriptase inhibitor (NNRTI) drug concentrations are reduced.

Table
Select CYP450 Inducers, Inhibitors, and Substrates

	1A2	2C19	2D6	3A4
Inducers	ritonavir rifampin phenytoin omeprazole phenobarbital nicotine	rifampin carbamazepine ritonavir efavirenz	rifampin phenytoin phenobarbital carbamazepine	efavirenz nevirapine rifampin phenytoin phenobarbital carbamazepine glucocorticoids St. John's Wort ritonavir

Table Select CYP450 Inducers, Inhibitors, and Substrates				
	1A2	**2C19**	**2D6**	**3A4**
				etravirine
Inhibitors	fluoroquinolones cimetidine ticlopidine fluvoxamine amiodarone atazanavir	cimetidine ketoconazole omeprazole fluoxetine lansoprazole paroxetine etravirine	ritonavir paroxetine sertraline fluoxetine cimetidine celecoxib amiodarone quinidine methadone	protease inhibitors (PIs) (in order of potency: ritonavir, indinavir, nelfinavir, amprenavir, atazanavir, saquinavir) delavirdine fluconazole ketoconazole itraconazole amiodarone diltiazem fluvoxamine nefazodone fluoxetine clarithromycin erythromycin posaconazole grapefruit juice Seville orange juice
Substrates	haloperidol theophylline zileuton amitriptyline cyclobenzaprine olanzapine	nelfinavir lansoprazole omeprazole pantoprazole diazepam phenytoin voriconazole etravirine	metoprolol carvedilol codeine dextromethorphan tramadol venlafaxine	clarithromycin cyclosporine erythromycin alprazolam midazolam triazolam simvastatin lovastatin atorvastatin nifedipine nisoldipine felodipine PIs nevirapine efavirenz delavirdine sertraline bepridil propafenone

Table Select CYP450 Inducers, Inhibitors, and Substrates				
	1A2	**2C19**	**2D6**	**3A4**
				amiodarone flecainide irinotecan pimozide ergotamine etravirine maraviroc

HAART-Related Drug Interactions

Anticonvulsants

Clinicians should monitor anticonvulsant levels in patients taking concurrent HAART and anticonvulsant therapy.

Clinicians should avoid prescribing carbamazepine, phenobarbital, and phenytoin for patients receiving non-nucleoside reverse transcriptase inhibitors (NNRTIs) or PIs. Valproic acid or levetiracetam may be considered.

Antifungal Drugs

Clinicians should not prescribe voriconazole for patients taking ritonavir (400 mg every 12 hours). Clinicians should avoid or use caution when combining voriconazole with the other NNRTIs or unboosted PIs.

Antimycobacterial Drugs

Clinicians should not use rifampin with any PI. Consider rifabutin with proper dose adjustment.

With proper dose adjustments, **rifampin** can be safely used with the following drugs:	
• Nucleotide reverse transcriptase inhibitors (NtRTIs) • Enfuvirtide • Maraviroc	• Efavirenz + nucleoside reverse transcriptase inhibitors (NRTIs) or NtRTIs
With proper dose adjustments, **rifabutin** can be safely used with the following drugs:	
• NRTIs • NtRTIs	• Lopinavir + ritonavir • Maraviroc

• Amprenavir • Atazanavir • Darunavir + ritonavir • Enfuvirtide • Etravirine • Fosamprenavir • Indinavir	• Nelfinavir • Raltegravir (no data; may be considered with close monitoring) • Ritonavir • Efavirenz when used with 2 NRTIs • Nevirapine when used with 2 NRTIs • Saquinavir + ritonavir • Tipranavir + ritonavir

Erectile Dysfunction Agents

The following is generally recommended when erectile dysfunction agents are combined with PIs:

Sildenafil - use reduced initial dose of 25 mg every 48 hours and monitor for adverse effects

Tadalafil - use initial dose of 5 mg, and do not exceed a single dose of 10 mg in 72 hours

Vardenafil - use initial dose of 2.5 mg, and do not exceed a single 2.5-mg dose in 72 hours

Ergot Alkaloids

Clinicians should not prescribe ergotamine derivatives in patients receiving concurrent PI therapy. Alternative medications should be considered.

Herbal Therapy

In the setting of PI- or NNRTI-based HAART, supplemental garlic and St. John's Wort are contraindicated.

All herbal products should be used with caution until further data are available regarding their effects with concurrent HAART.

Key Point:

Because most providers cannot accurately predict which patients use herbal therapy, it is important to discuss ARV/herbal drug interactions with all patients.

Hydroxymethyl Glutaryl Coenzyme A (HMG-CoA) Reductase Inhibitors

Clinicians should not prescribe simvastatin or lovastatin for patients taking PIs.

Key Points:

- Lovastatin and simvastatin are contraindicated with all PIs and delavirdine (DLV).
- Pravastatin is the safest drug for treating hyperlipidemia during concurrent PI therapy.
- Atorvastatin can be used cautiously at lower doses (5 to 10 mg) with careful titration.
- Rosuvastatin can be used at lower doses (5mg) with careful titration.

Oral Contraceptives

Clinicians should use caution when prescribing oral contraceptives for patients receiving HAART because of the variations in effect on ethinyl estradiol levels.

Clinicians should advise women who are taking efavirenz, nevirapine, lopinavir/ritonavir, nelfinavir, ritonavir, tipranavir/ritonavir, darunavir/ritonavir, or saquinavir to use alternate or additional forms of birth control.

Psychotropic Therapies

Drug interactions with most psychotropic therapies are summarized in Table 3 in the original guideline document.

Sedative/Hypnotics

Clinicians should not prescribe alprazolam, midazolam, or triazolam for patients receiving PIs. Lorazepam or oxazepam may be considered.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Identification of risk, prevention, and appropriate management of human immunodeficiency virus (HIV) drug-drug interactions

POTENTIAL HARMS

Refer to the "Major Recommendations" field above and to Appendix A in the original guideline document for specific cautions concerning various drug combinations.

CONTRAINDICATIONS

CONTRAINDICATIONS

Refer to the "Major Recommendations" field above and to Appendix A in the original guideline document for specific contraindicated drug combinations.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The AIDS Institute's Office of the Medical Director directly oversees the development, publication, dissemination and implementation of clinical practice guidelines, in collaboration with The Johns Hopkins University, Division of Infectious Diseases. These guidelines address the medical management of adults, adolescents and children with HIV infection; primary and secondary prevention in medical settings; and include informational brochures for care providers and the public.

Guidelines Dissemination

Guidelines are disseminated to clinicians, support service providers and consumers through mass mailings and numerous AIDS Institute-sponsored educational programs. Distribution methods include the HIV Clinical Resource website, the Clinical Education Initiative, the AIDS Educational Training Centers (AETC) and the HIV/AIDS Materials Initiative. Printed copies of clinical guidelines are available for order from the NYSDOH Distribution Center for providers who lack internet access.

Guidelines Implementation

The HIV Clinical Guidelines Program works with other programs in the AIDS Institute to promote adoption of guidelines. Clinicians, for example, are targeted through the Clinical Education Initiative (CEI) and the AIDS Education and Training Centers (AETC). The CEI provides tailored educational programming on site for health care providers on important topics in HIV care, including those addressed by the HIV Clinical Guidelines Program. The AETC provides conferences, grand rounds and other programs that cover topics contained in AIDS Institute guidelines.

Support service providers are targeted through the HIV Education and Training initiative which provides training on important HIV topics to non-physician health and human services providers. Education is carried out across the State as well as through video conferencing and audio conferencing.

The HIV Clinical Guidelines Program also works in a coordinated manner with the HIV Quality of Care Program to promote implementation of HIV guidelines in New York State. By developing quality indicators based on the guidelines, the AIDS Institute has created a mechanism for measurement of performance that allows

providers and consumers to know to what extent specific guidelines have been implemented.

Finally, best practices booklets are developed through the HIV Clinical Guidelines Program. These contain practical solutions to common problems related to access, delivery or coordination of care, in an effort to ensure that HIV guidelines are implemented and that patients receive the highest level of HIV care possible.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

New York State Department of Health. HIV drug-drug interactions. New York (NY): New York State Department of Health; 2008 Mar. 48 p. [32 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 (revised 2008 Mar)

GUIDELINE DEVELOPER(S)

New York State Department of Health - State/Local Government Agency [U.S.]

SOURCE(S) OF FUNDING

New York State Department of Health

GUIDELINE COMMITTEE

Medical Care Criteria Committee

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: New York State Department of Health. HIV drug-drug interactions. New York (NY): New York State Department of Health; 2007 Feb. 44 p.

GUIDELINE AVAILABILITY

Electronic copies: Available from the New York State Department of Health AIDS Institute Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Appendix A: drug interactions between antiretrovirals and other drugs. New York (NY): New York State Department of Health; 2008 Mar. Electronic copies: Available from the New York State Department of Health AIDS Institute Web site.
- Appendix B: routes of elimination of HAART and the effect on CYP450. New York (NY): New York State Department of Health; 2008 Mar. Electronic copies: Available from the New York State Department of Health AIDS Institute Web site.

This guideline is also available as a Personal Digital Assistant (PDA) download from the New York State Department of Health AIDS Institute Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on January 17, 2005. This summary was updated on April 15, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration (FDA) advisories on Sustiva (efavirenz) and COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on July 15, 2005 following the FDA advisory on Cialis, Levitra, and Viagra. This NGC summary was updated by ECRI Institute on September 18, 2007. This summary was updated by ECRI Institute on November 6, 2007, following the updated U.S. Food and Drug Administration advisory on Viagra, Cialis, Levitra, and Revatio. This summary was updated by ECRI Institute on March 28, 2008, following the FDA advisory on Prezista (darunavir). This NGC summary was updated most recently by ECRI Institute on June 5, 2008.

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